I. AMENDMENTS

A. In the Claims

Please amend claims 1, 45 and 46 as indicated in the listing of claims.

The listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

Claim 1. (Currently Amended) A method of generating a humanized mouse, comprising:

recombining a first DNA construct with a second DNA construct,

wherein the first DNA construct has a mouse DNA sequence contained therein, and

wherein the second DNA construct has a human DNA sequence contained therein and the human DNA sequence is flanked by a first and a second mouse DNA sequence that allows for recombination,

wherein the first and second mouse DNA sequences are orthologous to and have the same order and orientation relative to the human DNA sequence as human sequences flanking the human DNA sequence when it is present in the genome of a human;

isolating an intermediate homologously recombined [~~third~~] DNA construct having the human DNA sequence flanked by the first and second mouse DNA sequences and recombining the intermediate homologously recombined DNA construct with a third construct that has a mouse DNA sequence contained therein thereby generating a fourth DNA construct having a human sequence flanked by mouse sequences;

introducing the recombined ~~third~~ fourth DNA construct into a mouse embryogenic stem cell;

introducing the embryogenic stem cell into a mouse blastocyst, thereby producing a chimeric blastocyst; and

implanting the chimeric blastocyst into a pseudopregnant mouse, wherein the pseudopregnant mouse delivers a humanized mouse, thereby generating a humanized mouse.

Claim 2. (Cancelled)

Claim 3. (Original) The method of claim 1, wherein the first DNA construct is a bacterial artificial chromosome.

Claim 4. (Original) The method of claim 1, wherein the second DNA construct is a bacterial artificial chromosome.

Claim 5. (Original) The method of claim 4, wherein the bacterial artificial chromosome is linearized.

Claim 6. (Original) The method of claim 1, wherein the recombining is carried out in a strain of *E. coli*.

Claim 7. (Original) The method of claim 1, wherein the *E. coli* is deficient for *sbcB*, *sbcC*, *recB*, *recC* or *recD* activity and has a temperature sensitive mutation in *recA*.

Claim 8. (Previously presented) The method of claim 1, wherein the human DNA sequence is selected from the group consisting of a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer suppressor gene, a viral receptor gene, a bacterial receptor gene, a P450 gene, an insulin receptor gene, an immunoglobin gene, a metabolic pathway gene, a transcription factor gene, , a cytokine gene, a cell signaling pathway gene and a cell cycle gene.

Claim 9. (Original) The method of claim 1, wherein the third DNA construct is a bacterial artificial chromosome.

Claim 10. (Original) The method of claim 1, wherein the human DNA sequence is a human gene sequence having at least one intron contained therein.

Claim 11. (Previously Presented) The method of claim 10, wherein the third DNA construct has a selection marker contained within the at least one intron.

Claim 12. (Original) The method of claim 11, wherein the selection marker is added following the recombining step.

Claim 13. (Original) The method of claim 11, wherein the selection marker is a positive selection marker.

Claim 14. (Previously Amended) The method of claim 11, wherein the third DNA construct has a second selection marker that flanks the first or the second mouse DNA sequence.

Claim 15. (Cancelled)

Claim 16. (Previously Presented) The method of claim 1, wherein the human DNA sequence comprises a coding sequence comprising a start codon having a 5' end, and the first mouse DNA sequence in the second construct is joined to the human DNA coding sequence at the 5' end of the start codon.

Claim 17. (Previously Presented) The method of claim 16, wherein the human DNA coding sequence comprises a stop codon having a 3' end, and the second mouse DNA sequence in the second construct is joined to the human DNA coding sequence at the 3' end of the stop codon.

Claim 18. (Previously Presented) A linearized bacterial artificial chromosome DNA construct for performing homologous recombination within a cell of a non-human animal, the construct comprising:

a human DNA coding sequence having at least one intron disposed therein;

a selection marker gene contained within said at least one intron;

a first non-human animal DNA sequence and a second non-human animal DNA sequence, wherein said first and second non-human animal DNA sequences flank the human DNA coding sequence,

wherein the first and second non-human animal DNA sequences are from the same species,

wherein the first and second non-human animal DNA sequences are orthologous to and have the same order and orientation relative to the human DNA sequence as human sequences flanking the human DNA sequence when it is present in the genome of a human.

Claim 19. (Original) The DNA construct of claim 18, further comprising a second selection marker adjacent to one of the non-human DNA sequences.

Claim 20. (Cancel)

Claim 21. (Original) The DNA construct of claim 18, wherein the first and second non-human DNA sequences are mouse genomic DNA sequences.

Claim 22. (Previously Presented) The DNA construct of claim 18, wherein the non-human animal DNA sequences are from about 0.1 to 200 kb in length.

Claim 23. (Previously Presented) The DNA construct of claim 18, wherein the human DNA comprises a coding sequence comprising a start codon having a 5'end and the first non-human sequence is joined adjacent to the 5' end of the start codon of the human DNA coding sequence.

Claim 24. (Previously Presented) The DNA construct of claim 23, wherein the human DNA coding sequence comprises comprises a stop codon having a 3' end and the first non-human sequence is joined adjacent to the 3' end of the stop codon of the human DNA coding sequence.

Claim 25. (Previously Presented) A method for generating a DNA construct for performing homologous recombination within a cell by

recombining a first DNA construct with a second DNA construct, wherein the first DNA construct has a non-human animal DNA sequence contained therein,

wherein the second DNA construct has a human DNA sequence contained therein and the human DNA sequence is flanked by a first and a second non-human animal DNA sequence,

wherein the non-human animal DNA sequences of the first and second construct are from the same species,

wherein the first and second non-human animal DNA sequences are orthologous to and have the same order and orientation relative to the human DNA sequence as human sequences flanking the human DNA sequence when it is present in the genome of a human; and

isolating a homologously recombined third DNA construct having the human DNA sequence flanked by the first and second non-human animal DNA sequence.

Claim 26. (Cancelled)

Claim 27. (Original) The method of claim 25, wherein the first DNA construct is a bacterial artificial chromosome.

Claim 28. (Original) The method of claim 25, wherein the second DNA construct is a bacterial artificial chromosome.

Claim 29. (Original) The method of claim 28, wherein the bacterial artificial chromosome is linearized.

Claim 30. (Original) The method of claim 25, wherein the recombining is carried out in a strain of *E. coli*.

Claim 31. (Original) The method of claim 25, wherein the *E. coli* is deficient for *sbcB*, *sbcC*, *recB*, *recC* or *recD* activity and has a temperature sensitive mutation in *recA*.

Claim 32. (Previously Presented) The method of claim 25, wherein the human DNA sequence is selected from the group consisting of a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer suppressor gene, a viral receptor, a bacterial receptor gene, a P450 gene gene, an insulin receptor gene, an immunoglobin gene, a metabolic pathway gene, a transcription factor gene, , a cytokine gene, a cell signaling pathway gene and a cell cycle gene.

Claim 33. (Original) The method of claim 25, wherein the third DNA construct is a bacterial artificial chromosome.

Claim 34. (Original) The method of claim 25, wherein the human DNA sequence is a human gene sequence having at least one intron contained therein.

Claim 35. (Previously Presented) The method of claim 34, wherein the third DNA construct has a selection marker contained within the at least one intron.

Claim 36. (Original) The method of claim 35, wherein the selection marker is added following the recombining step.

Claim 37. (Original) The method of claim 35, wherein the selection marker is a positive selection marker.

Claim 38. (Previously Presented) The method of claim 35, wherein the third DNA construct has a second selection marker that flanks the first or the second non-human animal DNA sequence.

Claim 39. (Previously Presented) The method of claim 25, wherein the human DNA sequence comprises a coding sequence comprising a start codon having a 5' end, and the first non-human DNA sequence in the second construct is joined to the human DNA coding sequence at the 5' end of the start codon.

Claim 40. (Previously Presented) The method of claim 39, wherein the human DNA coding sequence comprises a stop codon having a 3' end, and the second non-human DNA sequence in the second construct is joined to the 3' of the stop codon.

Claim 41. (Previously Presented) A humanized mouse produced by the method of claim 1, wherein the human DNA sequence is a gene selected from a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer suppressor gene, a viral receptor gene, a bacterial receptor gene, a P450 gene, an insulin receptor gene, an immunoglobin gene, a metabolic pathway gene, a transcription factor gene, , a cytokine gene, a cell signaling pathway gene and a cell cycle gene.

Claim 42. (Cancelled)

Claim 43. (Previously Presented) The humanized mouse of claim 41, wherein the gene is involved in human drug metabolism.

Claim 44. (Previously Presented) The humanized mouse of claim 41, wherein the gene is a PXR, , RXR, CYP3A4, CYP2B6, CYP2C9 or MDR1 gene.

Claim 45. (Currently Amended) A method of generating a humanized cell, comprising:

recombining a first DNA construct with a second DNA construct,
wherein the first DNA construct has a non-human animal DNA sequence contained therein, and
wherein the second DNA construct has a human DNA sequence contained therein and the human DNA sequence is flanked by a first and a second non-human animal DNA sequence,
wherein the first and second non-human animal DNA sequences are from the same species,
wherein the first and second non-human animal DNA sequences are orthologous to and have the same order and orientation relative to the human DNA sequence as human sequences flanking the human DNA sequence when it is present in the genome of a human;

isolating an intermediate homologously recombined third DNA construct having a the human DNA sequence flanked by the first and second non-human animal DNA sequence and recombining the intermediate homologously recombined DNA construct with a third construct that has a mouse DNA sequence contained therein thereby generating a fourth DNA construct having a human sequence flanked by mouse sequences; and

introducing the recombined ~~third~~ fourth DNA construct into a non-human animal cell of the same species as the non-human DNA sequences of the first and second constructs, thereby generating a humanized cell.

Claim 46. (Currently Amended) The method of claim 45, wherein the non-human animal cell is a mouse embryogenic stem cell.

Claim 47. (Previously Presented) A DNA construct for performing homologous recombination within a cell of a non-human animal, the construct comprising:

a human DNA coding sequence having at least one intron disposed therein;

a selection marker gene contained within said at least one intron;

a first non-human animal DNA sequence and a second non-human animal DNA sequence,

wherein said first and second non-human animal DNA sequences flank the human DNA coding sequence,

wherein the first and second non-human animal DNA sequences are from the same species,

wherein the first and second non-human animal DNA sequences are orthologous to and have the same order and orientation relative to the human DNA sequence as human sequences flanking the human DNA sequence when it is present in the genome of a human; and

a second selection marker adjacent to one of the non-human DNA sequences.

Claim 48. (Previously Presented) The DNA construct of claim 47, wherein the construct is a linearized bacterial artificial chromosome.

Claim 49. (Previously Presented) The DNA construct of claim 47, wherein the first and second non-human DNA sequences are mouse genomic DNA sequences.

Claim 50. (Previously Presented) The DNA construct of claim 47, wherein the non-human animal DNA sequences are from about 0.1 to 200 kb in length.

Claim 51. (Previously Presented) The DNA construct of claim 47, wherein the human DNA sequence comprises a coding sequence comprising a start codon having a 5'end and the first non-human sequence is joined adjacent to the 5' end of the start codon of the human DNA coding sequence.

Claim 52. (Previously Presented) The DNA construct of claim 51, wherein the human DNA coding sequence comprises a stop codon having a 3' end and the first non-human sequence is joined adjacent to the 3' end of the stop codon of the human DNA coding sequence.